Tropical diseases
On the road to success

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In April last year, six medical researchers from several parts of Asia and Latin America met at the World Health Organization (WHO) Malaria Training Centre in Prabudhapat, a small town in rural Thailand. They were joined there by Dr Karl B. Rieckmann, a well-known parasitologist at the University of New Mexico in Albuquerque, USA.

For two weeks, in a library turned laboratory and sporadically isolated from the humid hot weather by a reluctant air conditioner, the researchers poured over hundreds of microscope slides with blood samples taken from malaria patients in the region and incubated with different antimalarial drugs. On the door of the library, someone had posted a sign: “On the road to success.”

The purpose of the gathering was to assess a new technique developed by Dr Rieckmann for measuring the susceptibility of malaria parasites to drugs. Such measurement must be an essential part of the effort to control malaria as it helps identify those strains of the *Plasmodium* parasite that have become resistant to chloroquine, hitherto the standard and most effective treatment. Resistance of the parasite to chloroquine and related drugs has been reported in 20 countries, including Thailand.

Until now, the only method for identifying those mutant parasites with certainty required the use of several cc of blood drawn from a patient’s vein, a method that required experienced personnel to collect the samples and one that could not be practiced routinely on young children because of the large amount of blood required. But three months earlier, in January 1978, Dr Rieckmann had published the description of a new technique based on the microscope study of a single drop of blood from a finger prick. This *in vitro* microtechnique, if it turned out to be reliable and practicable on a large scale, could represent a major contribution to the diagnosis of drug-resistant malaria and possibly also to the screening of new drugs.

The assessment of such a method could have taken months, even years. The organization of the WHO Special Programme for Research and Training in Tropical Diseases made it possible, however, to reduce this lead time to a few weeks. In fact, in two weeks of intensive work — often carried on late into the evening — the team showed that a single drop of blood, maintained in an appropriate medium to which varying concentrations of drugs were added, made it possible to identify drug resistant parasites with as much reliability as the earlier, more cumbersome technique.

The results were encouraging but still inconclusive. In the months that followed, the researchers continued testing the technique in endemic regions of Asia and Latin America, and trained other researchers in its use. By August of 1976 (five months after the meeting in Thailand), courses in parasite sensitivity had been given in Brazil, Colombia, El Salvador, Sudan, Bangladesh, India, and Sri Lanka, and a test kit was being prepared for field testing.

At the same time as the researchers were working in Prabudhapat, another Special Programme activity was underway at Mahidol University in Bangkok. There, Professor William Trager of Rockefeller University was giving courses in another new technique that required sents one of the few genuine breakthroughs to have occurred in the field of parasitology in the past few years: the continuous *in vitro* culture of malaria parasites.

The breakthrough came in 1976 when Prof. Trager succeeded in maintaining a lab culture of *Plasmodium falciparum*, the deadliest of the malaria parasites, for several months. In the months that followed, his method was tried with success by a number of parasitologists. For the first time, large quantities of the parasite could be made available for research purposes, opening the way to the development of a vaccine. The possibility of developing a vaccine is one of the greatest hopes of malaria research. Experiments on animals and a few trials on human volunteers have shown that at least a partial immunity against the disease can be acquired.

Some 20 researchers, most of them from Asian countries, availed themselves of Prof. Trager’s visit. And taking advantage of this “international première”, the university set up assorted courses in parasite genetics, assessment of drug resistance, and seminars on the typing of different strains of parasites with the help of WHO. The scientists who participated have since held a course for their colleagues. Meanwhile, Prof. Trager held a repeat performance at the University College of Ibadan, Nigeria.

This renewal of interest in malaria and other tropical diseases dates from 1975 or 1976 when the increasing...
burden of the diseases was recognized by many governments and international organizations, and when efforts at controlling them failed in many countries. The Special Programme for Research and Training in Tropical Diseases was established by WHO in order to coordinate the efforts of scientists throughout the world in an assault of countries. The Special Programme may be of a limited duration. It will not in itself solve the problems posed by tropical diseases deeply entrenched in many regions of the world. It must, however, promote national commitment, the establishment of research and training institutions, and the career and salary structures needed for the support of scientific capabilities over the long term.

To this end, a Research Strengthening Group has been set up to effect a mutually beneficial union of modern science and research in the tropics. Organized as aSWG, it has initiated collaboration between institutions in the developing and developed world, and between institutions within the developing countries, in order to promote a scientific approach to problem solving and the mastery of the needed technology. The Programme can contribute the backing of top international scientists and financial support. Institutions and scientists from industrialized countries may help train researchers from developing countries. Institutions in developing countries may also be strengthened in certain areas. For instance, a training course leading to a master's degree in tropical diseases with emphasis on clinical aspects will be given at the University of Nairobi in Kenya. A proposal for the creation of a Centre for Research and Training in Clinical Pharmacology has been approved at the University of Ibadan, Nigeria, and the Institute for Medical Research in Kuala Lumpur, Malaysia, will be strengthened in tropical diseases.

Socioeconomic aspects of tropical diseases, long neglected, are an integral part of the Programme. In fact, it is recognized that biomedical and applied research must be accompanied by social science research geared to improving the application of existing technologies, and to preparing the way for the choice and the successful application of new ones.

Yet this is a practically uncharted field of inquiry. New analytical methods and approaches are needed to help prepare guidelines for a feasible policy of disease control that can be implemented with means available in developing countries. They can help in indicating what a country can do with a given budget, what are the best strategies to choose, what basic information is still missing, and what could be expected from other approaches. Two Scientific Working Groups will be particularly concerned with the human and economic factors that play an important role in disease transmission. Both are expected to lead to the development of quantitative analytic techniques that should yield results useful in an "operational research" approach to be developed in parallel with new biomedical tools.

The firstSWG to be set up focused on the immunology of leprosy, a disease that affects some 10 million people in the world. Considerable progress has been made, including the discovery that nine-banded armadillos thrive best on tinned cat food. This finding may seem insignificant to some, but not to the researchers. The SWG had found that large amounts of the leprosy bacillus, Mycobacterium leprae, can be obtained by injecting

Researchers collect samples from the Monongo River in Ivory Coast in order to study the breeding ground and habitat of the blackfly, vector of river blindness.
the infective material into the armadillo. Previously, only small amounts could be gathered following injection into foot pads of mice. But a major problem to standardizing and increasing production was that the armadillos died before the bacillus could reproduce in large amounts. They died, not of infection, but of malnutrition because laboratory workers didn’t quite know what diet the captive animals thrive. Thus, the cat food finding became part of the picture of leprosy research.

The availability of large amounts of infective material enabled the members of the group to carry out experiments on mice and guinea pigs, and to show that in these animals M. leprae inoculum was indeed capable of eliciting long term protection against infection with live M. leprae. The results were confirmed by several laboratories and the study is now underway of different possible strategies for the development and testing of an actual leprosy vaccine.

In the meanwhile, the group concerned with the chemotherapy of leprosy has completed the task of designing several test protocols to study the treatment of leprosy with existing drugs. Trials are being carried out in four centres, two in India, one in Africa and one in the Soviet Union.

Finally, a new group is being formed to study the fundamental biology of the bacillus. It will attempt to establish cultures of the bacillus in vitro, and will utilize the most modern techniques of biomedical science, including genetic engineering.

Of the six diseases that are the target of the Special Programme, five are vector-borne: trypanosomiasis, malaria, filariasis, leishmaniasis, and schistosomiasis. In the case of trypanosomiasis or sleeping sickness, no vector control treatment or prevention measure exists that can eradicate the disease. At best, partial suppression can be achieved, and it requires relentless efforts. In the first half of this century, continuous medical surveillance programs gradually reduced the incidence of the disease, but in the 1960s it gained strength, particularly in Angola, Cameroon, the Sudan, and regions of Kenya.

One of the most important goals of the Special Programme is to provide assistance and guidance to improve surveillance. This is being done through leadership seminars to train and motivate medical assistants and veterinary assistant. The surveillance system strives to improve the existing means of control to make their utilization simple and less costly. Several new diagnostic methods are being tested, notably an “instant flocculation test” requiring a single drop of blood to show the antigen-antibody reaction that means infection has taken place. Standardized treatment protocols using existing drugs are being developed and new compounds tested. A few such compounds have been identified through research supported by the Programme, and additional screening and testing is carried out in cooperation with the pharmaceutical industry.

Interesting results have been achieved with a new low-volume method of spraying insecticides: the chemicals are broken down into tiny aerosol-like droplets and delivered from the air by helicopters, thus achieving a considerable saving of costly chemicals.

The Programme also supports empirical research of control agents and the screening of potentially useful new compounds, as well as fundamental research requiring the study of the metabolic processes of the trypanosome parasite, its relationship with the host, and the immunological processes involved.

Filariasis is also on the increase. This disease, or rather group of diseases (at least eight filarial parasites infect humans), is not well understood. People have different reactions to it, the relationship between the host’s immune response to the invading parasite and the antigens of the parasite remains a puzzle. None of the parasites have been cultured in the laboratory, and only a few have been grown in animals. The picture is further complicated by the fact that the parasites go through different life stages.

Regular meetings of the Filariasis Scientific Working Group and Steering Committee have led to the identification of research priorities and a score of specific projects have been outlined.

Mosquitoes, flies, snails... these are major vectors in tropical diseases, in dispensable links in the chain of transmission. Breaking the links would interrupt the cycle, but it has been shown that it is not possible within the foreseeable future. Vector control remains, nevertheless, an important weapon in the struggle, and biological control methods a promising avenue.

Now that pesticide costs are climbing ever higher, and many vectors have become resistant to major pesticides, research is under way of finding other means, notably bacteria and fungi, to attack the vectors. This approach is by no means new to the WHO, nor is it limited to the Special Programme. Since 1965, Ohio State University has been collaborating with WHO in conducting a global inventory of likely candidates and this effort has now been intensified.

Several promising agents have been identified, notably spore-forming bacteria. For example, in India a particular strain of the bacillus Thuringensis has been shown to be effective, at least in laboratory tests, against two species of mosquitoes. Viruses, insect-derived fungi, protozoa, and nematode worms are also promising candidates, but much work remains to be done before suitable ones are identified, and tested in large-scale field trials.

The Special Programme for Research and Training in Tropical Diseases does not claim to be able to solve, within a foreseeable future, the health problems that are particular to the tropical regions of the world. But the fact that the Programme exists is a sign that its activities are expanding, and that it is receiving increasing support from national governments and international agencies that there is a global recognition of a problem that cannot be solved by the mere transfer of medical technology to the developing world.

The Programme’s ambition is to become a tool that scientists can rely on to communicate and collaborate on a global scale towards easing the tremendous burden posed by tropical diseases. It may be said that the investment is relatively small in comparison to the dimensions of the problem. But there is an attempt to create a chain of transmission of knowledge with a multiplier effect. If this succeeds, every country will have its own qualified task force to deal with its own problems, as well as the backup of the international scientific community.